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Hornemann, Th

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Mini review: Lipids in Peripheral Nerve Disorders

Th. Hornemann

Institute for Clinical Chemistry, University Hospital and University Zurich, 8091, Zürich, Switzerland

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ABSTRACT

Neurons are polarized cells whose fundamental functions are to receive, conduct and transmit signals. In bilateral animals, the nervous system is divided into the central (CNS) and peripheral (PNS) nervous system. The main function of the PNS is to connect the CNS to the limbs and organs, essentially serving as a relay between the brain and spinal cord and the rest of the body. Sensory axons can be up to 3 feet in length. Because of its long-reaching and complex structure, the peripheral nervous system (PNS) is exposed and vulnerable to many genetic, metabolic and environmental predispositions. Lipids and lipid intermediates are essential components of nerves. About 50 % of the brain dry weight consist of lipids, which makes it the second highest lipid rich tissue after adipose tissue. However, the role of lipids in neurological disorders in particular of the peripheral nerves is not well understood. This review aims to provide an overview about the role of lipids in the disorders of the PNS.

1. Introduction

About 20 % of the medical consultation in adults are because of chronic neurologic diseases [82] and the evaluation of sensory disturbances are one of the five most common reasons for neurologic examinations [60]. The prevalence of peripheral neuropathy in the general population is 2.4 % and increases to an estimated 8 % for those over 55 years of age [1,54].

The PNS consists of several components that include motor, sensory, and autonomic neurons with their afferent or efferent axons, myelinating and non-myelinating Schwann cells, connective tissue components (endoneurium, perineurium, epineurium), and blood/lymphatic vessels. The cell bodies of sensory neurons are located in the DRGs and are not protected by the blood–brain barrier.

1.1. Lipid composition of neurons

Mammalian cells comprise thousands of chemically distinct lipids. Lipids can be generally classified into eight families: glycerophospholipids, sphingolipids, glycerolipids, sterol lipids, free fatty acids, prenol lipids, saccharolipids, and polyketides [25,26]. For most lipids, their functions depend on the molecular structure and can be very different for the various classes and even for different lipid species within the same class [83].

To understand the role of lipids in neuronal pathology, it is important to look at myelin and neurons as closely connected anatomical and functional units. Unfortunately, little is known on the lipid composition of neurons and their differences in the individual neuronal compartments.

The dry weight of the neuronal soma contains about 37 % of lipids in total, of which the major classes are phospholipids (57.1 %), cholesterol (15.4 %) and galactolipids (4.8 %) [13]. Other lipid species that are found in soma are ceramide, glucosylceramides or triglycerides (Fig. 1). The major phospholipids are PC and PE. Abundant within the group of galactolipids are cerebrosides and sulfatides, which are typically found in a molar ratio of 2:1. The neuronal soma also contains tetrasialo (GT)-, disialo (GD)- and monosialogangliosides (GM). In contrast to soma, neurites contain only 15 % of the dry weight as lipids. They have about the same relative content of phospholipids (56.4 %) but higher levels of cholesterol (22.1 %) and galactolipids (7.7 %). Also the content of sphingomyelin and PS is higher in neurites and the ganglioside pattern consists entirely of gangliosides GQ1b, GT1b, GD1b, GD1a, and GD3, with no monosialogangliosides [13]. Gangliosides are sphingolipids and formed from ceramides by the transfer of a glucose or galactose molecule to generate glucosylceramide (GluCer) and galactosylceramide (GalCer). These metabolites are then transformed further into complex gangliosides and sulfatides respectively (Fig. 1). Typically, gangliosides contain an oligosaccharide head structure with one or more sialic acid (e.g. N-acetyl-neuraminic acid). They constitute a large family of lipids with more than 100 different species, of which GM1, GD1a, GD1b and

Abbreviations: PE, phosphatidylethanolamine; PC, phosphatidylcholine; PS, phosphatidylserine; MBP, myelin binding protein; Cer, ceramide; 1-deoxySL, 1-deoxysphingolipid; SPT, serine palmitoyltransferase; T1DM, diabetes type 1; T2DM, diabetes type 2.

E-mail address: thorsten.hornemann@usz.ch.

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GT1b account for 96 % of the gangliosides in the human brain [74]. Neurites in contrast, consist entirely of GQ1b, GT1b, GD1b, GD1a, and GD3, without any monosialogangliosides (GM) present [13]. It was long presumed that all axonal membrane lipids are synthesized within the cell body and moved by anterograde transport into the axons for axonal extension. However, more recent data indicated that axons are able to perform at least some aspects of lipid metabolism by themselves [89].

1.2. Lipid composition of myelin

Axons are surrounded by segments of myelin sheaths, which are lipid-rich multilamellar stacks of membranes. The main function of myelin is to insulate the axon and to cluster sodium channels into the nodes of Ranvier to allow for saltatory conduction of action potentials [77]. Myelin is formed by oligodendrocytes in the central (CNS) and by Schwann cells in the peripheral nervous systems (PNS) of vertebrates. The lipid composition of myelin is well investigated and varies significantly from neurons and other biological membranes. During the active phase of myelination, glia-forming cells generate large amounts of lipids in a relatively short period. The most abundant lipid classes in myelin are cholesterol, galactosylceramide and ethanolamine plasmalogens [62] Together, these three classes comprise for 65 % of the total lipid dry weight. For most cellular membranes, is the molar ratio of cholesterol, phospholipids and glycosphingolipids about 25:65:10 (mol %) whereas the molar ratios in myelin are in the range of 40:40:20 (mol %) [62]. Cholesterol is an essential structural lipid and provides stability to myelin by regulating both fluidity and permeability of the membrane and is required for myelin growth and compaction. Electron microscopy analysis of mice lacking cholesterol biosynthesis in Schwann cells, reveals severe hypomyelination with stretches of uncompacted myelin [55].

Galactosylceramides and sulfatides with long chain fatty acid moieties, in particular 24:0 and 24:1 fatty acids, are the most abundant SL's in myelin. The final step in the synthesis of galactosylceramide is carried out by the UDP-galactose:ceramide galactosyltransferase (CGalT), which transfers UDP-galactose to ceramide [81]. For the synthesis of sulfatides, galactosylceramide must be transported to the Golgi where a 3-O-sulfation to the galactose residue takes place through the cerebroside sulfotransferase (CST) [9,86]. However, the inactivation of CGalT in myelinating Schwann cells did not result in any obvious alterations [73] whereas the inactivation of CGalT in neurons using Nestin-Cre resulted in a drastic phenotype. The animals showed progressive dysreflexia and motor defects and died within 24 days after birth [39]. Electron microscopy of peripheral nerves revealed extensive splitting and broadening of the myelin sheaths as well as axonal degeneration.

Given the abundance of galactosylceramides and their enrichment in myelin, it is surprising, that deleting CGalT does not impair myelin synthesis. Instead, CGalT-deficient oligodendrocytes partially compensated the loss of galactosylceramide by producing 2-hydroxlyated glucosylceramide, a lipid usually not present in myelin. The additional deletion of UDP-glucose ceramide glucosyltransferase (UGCG) in CGalT knockout mice deleted all glycosphingolipids in myelin but the dysmyelinating phenotype of CGalT −/− mice was not aggravated further [73]. Glycosphingolipids appear therefore not essential for the synthesis of compact myelin per se. Instead, these mice partially compensated the loss in glycosphingolipids by increasing the synthesis of 2-hydroxlyated sphingomyelin. Generally, more than 50 % of galactosylceramides and sulfatides are hydroxylated at the 2-C atom of the N-linked fatty acid. This reaction is catalyzed by the fatty acid 2-hydroxylase (FA2H) and seems to be important for strengthening the network of interconnecting hydrogen bonds [3,23,98]. FA2H-deficient mice that lack 2-hydroxylated glycosphingolipids form normal myelin initially, but the myelin sheaths degenerate at older age [98]. In humans, mutations in the FA2H gene are clinically associated with gait abnormalities, spastic quadriparesis, ataxia, and dystonia. FA2H mutations can also cause a form of hereditary spastic paraplegia and leukodystrophy.

Another distinguishing feature of myelin lipid composition is the high amount of ethanolamine plasmalogens. Plasmalogens contain a vinyl ether at the sn-1 position and an ester at sn-2 position. The sn-1 position typically contains saturated C16 (C16:0, C18:0) and monounsaturated C18:1 fatty acids, while the sn-2 position mostly contains polyunsaturated fatty acids, specifically arachidonic acid (C22:6) or docosahexaenoic acid (C20:4) [53]. Plasmalogens can protect unsaturated membrane lipids against oxidation by singlet oxygen [12] and have been shown to terminate oxidative chain reactions by stopping further lipid peroxidation [78].

2. Peripheral neuropathies

The pronounced polarity and length of the peripheral axons is most

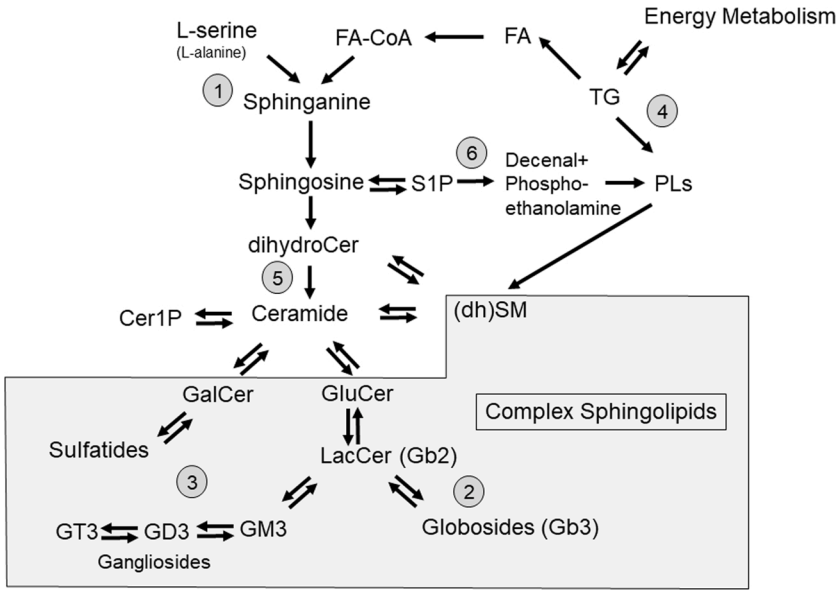

Fig. 1. Overview of the sphingolipid metabolism and the metabolic steps that were found to be associated with peripheral neuropathies . (1)HSAN1, (2) Fabry Disease, (3) GBS, (4) T2DM, (5) Leukodystrophy with PNP [42], (6) CMT [4].
Cer Ceramide; FA fatty acids; TG triglycerides; GalCer Galactosylceramide; GluCer Glucosylceramide; LacCer Lactosylceramide; (dh)SM (dihydro)Sphingomyelin.

likely a major reason for their vulnerability. The functionality of axons relies on the integrity of their perikaryon and on the connection with their peripheral targets (muscle, sensory end-organs, blood vessels, glands, etc.) as well as long distance axonal transport and continuous support from glial elements [59].

Peripheral neuropathies can be categorized into hereditary-, inflammatory-, neoplastic-, metabolic- and toxic neuropathies (see Table 1). Depending on the affected nerve component, they can be axonal, demyelinating, or mixed. However, axonal degeneration is predominant and in the majority of cases, followed by a demyelinating or mixed form [75].

If it comes to relevance of lipids in peripheral neuropathies, mostly the sphingolipid metabolism is involved (Fig. 1). Sphingolipids (SL) are a class of structurally highly diverse lipids and fundamental components of eukaryotic cell membranes. SL de-novo synthesis starts at the endoplasmic reticulum (ER) with the formation of a sphingoid base, which is the common structural element of all SLs. The sphingoid bases are then subsequently N-acylated with a fatty acid of variable length.

The class of sphingolipids encompasses hundreds of structurally different sub-species that are formed by multiple enzymes in a tissue and isozyme specific manner [56]. There are numerous sphingolipid species, which differ in their head group structure but also in carbon chain length, unsaturation and hydroxylation of both the sphingoid base and fatty acyl moieties [50].

2.1. Fabry disease

Given the high amount of sphingolipids present in neuronal tissue, it is not surprising that impairments in the SL metabolism are frequently associated with neuronal defects. Mutations in enzymes that catabolize SL cause lysosomal storage diseases (LSDs) including multisystem disorders such Nieman-Pick-Disease type C (NPC), Gaucher, Farbers or Tay-Sachs disease [65,76]. However, the neuronal manifestations of LSDs affect mostly the CNS rather than the PNS. An exception is Fabry disease that affects the PNS. Fabry disease is caused by mutations in the *GLA* gene that encodes for the lysosomal enzyme alpha-galactosidase A (aGalA) which degrades the glycosphingolipid globotriaosylceramide in the lysosomes. aGalA deficiency therefore leads to an accumulations of globotriaosylceramide in cells throughout the body, particularly cells lining blood vessels, skin, kidneys, heart and the nervous system. Fabry is a multisystem disorder affecting several organs involving potentially life-threatening complications such as progressive kidney damage, heart attack, and stroke. Characteristic features of Fabry disease are episodes of neuropathic pain, particularly in the hands and feet (acroparesthesias), angiokeratomas, hypohidrosis; corneal opacity or corneal verticillata; gastrointestinal problems, tinnitus and hearing loss.

GLA gene mutations that result in an absence of alpha-galactosidase A activity lead to the classic, severe form of Fabry disease whereas mutations that decrease but do not eliminate the enzyme's activity usually cause the milder, late-onset forms typically affecting only heart or kidneys. Besides conventional medical treatment intravenously administered enzyme replacement therapy (ERT) or oral chaperone therapy are current therapeutic options in Fabry. Substrate reduction therapy (SRT) by blocking the enzyme glucosylceramide synthase (GCS) is currently investigated as an alternative therapy in Fabry and other LSDs.

2.2. Hereditary peripheral neuropathies

Hereditary peripheral neuropathies can be divided into three major subgroups based on their predominant phenotype, such as hereditary motor and sensory neuropathies (HMSN or Charcot–Marie–Tooth (CMT) disease), hereditary sensory and autonomic (HSAN) and hereditary motor neuropathies (HMN). CMT is the most frequent hereditary neuromuscular disorder with an estimated cumulative prevalence of 1/2500 but showing a strong variation between populations [54]. The initial symptoms typically include a predominantly distal, progressive muscle weakness and wasting [32]. CMT1 includes dominantly inherited forms of demyelinating motor and sensory neuropathies. About 70–80 % of all CMT1 cases is caused by a duplication of the 17p11.2 locus containing *PMP22*, a major myelin protein gene [57].

In contrast, hereditary sensory and autonomic neuropathies are relatively rare, with an incidence of 1:25,000 [68]. Mutations in the sphingolipid degrading enzyme S1P-lyase (SGPL1) were associated with CMT [4]. In HSANs, primarily sensory and autonomic neurons are affected. The HSAN subtypes can be distinguished by the differential loss and/or regeneration of the different nerve fiber populations [43]. Axonal loss in both, myelinated and unmyelinated fibers, can be observed in HSAN patients with *ATL1* [29], *RAB7* [36], *DNMT1* [6] and F*AM134B* [49] mutations. Generally, unmyelinated fibers seem to be more affected in HSANs although in some cases such as in HSAN1 there is also slowing of conduction and segmental demyelination suggesting defects in myelination and/or the nodal complex [35].

HSAN1 is an autosomal and dominantly inherited axonal neuropathy with a heterogeneous clinical picture. Patients have prominent sensory abnormalities and the neurological phenotype is often complicated by severe infections, osteomyelitis, and amputations. Symptoms include loss of sensation in the feet, severe sensory loss in the upper and lower limbs, dysesthesia, distal muscle weakness, distal lower limb sensory loss with ulceration and osteomyelitis. Some individuals develop hearing loss [8,19,45,46,61,71,80].

HSAN1 has a variable onset with first symptoms being universally sensory and occurring at a median age of 20 years (range 14–54 years) [87]. HSAN1 is caused by several missense mutation in the *SPTLC1* or

Table 1
Peripheral Neuropathies.

Hereditary peripheral neuropathies	Inflammatory neuropathies	Neuropathies associated with neoplasias	Metabolic neuropathies	Toxic neuropathies
Charcot–Marie–Tooth (CMT) disease	**Guillain–Barre syndrome**	Paraneoplastic neuropathy	**Diabetic neuropathy**	Alcohol abuse
Hereditary sensory and autonomic neuropathy (HSAN)	Chronic inflammatory demyelinating polyneuropathy (CIDP)	Monoclonal gammopathy /	Neuropathy associated with thyroid gland dysfunction	**Chemotherapeutic agents**
hereditary motor neuropathies (HMN)	Vasculitis	POEMS syndrome	Uremic neuropathy	Alcohol abuse
Familial amyloid neuropathy	Celiac disease	Amyloidosis	Liver failure	Drugs
Polyglucosan body disease	Multifocal motor neuropathy Cryoglobulinemia		Vitamin deficiencies	

Classification of peripheral neuropathies (adapted from [43]). Peripheral neuropathies related to lipid disorder are shown in bold. POEMS: polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes.

SPTLC2 gene encoding for two subunits of the serine-palmitoyltransferase (SPT). Mutations in the *SPTLC1* are termed HSAN1A whereas mutation in *SPTLC2* are called HSAN1C although there is no obvious clinical difference between the two forms.

SPT catalyzes the first and rate-limiting step in the de-novo synthesis of sphingolipids [31,33,34], which starts with the conjugation of L-serine and palmitoyl-CoA to form sphinganine [37,85,92,97]. Aside from L-serine, the enzyme can also use alanine and glycine as alternative substrates. This alternate activity forms a category of atypical 1-deoxy--sphingolipids (1-deoxySL) that lack the C1-hydroxyl group of canonical SL [51,67]. This precludes their conversion into complex SLs (sphingomyelins and glycosphingolipids) but also prevents their terminal degradation by the S1P-lyase (SGPL1) [96].

The conjugation with L-alanine forms 1-deoxysphinganine (1-deoxySA), while the use of glycine forms 1-deoxymethylsphinganine (1-deoxymethylSA) [67,97].

Common to all HSAN1 mutations is the permanent shift in the substrate specificity of SPT from L-serine to L-alanine and glycine, which is about 20–30 fold increased compared to wild-type SPT [12,46]. Among several variants of unclear significance (VUS), eight missense mutations in SPTLC1 and four mutations in SPTLC2 have been conclusively linked to HSAN1 [11].

Elevated 1-deoxySL levels were confirmed in HSAN1 mutant expressing cell lines, primary patient cells (lymphocytes and fibroblasts) as well as in a transgenic HSAN1 mouse model [24,28] and in HSAN1 patient plasma [67]. Plasma 1-deoxySL levels correlate with disease severity based on the Charcot-Marie-Tooth Examination Score (CMTES). Natural history studies revealed that total 1-deoxySL plasma concentrations can vary significantly between individual HSAN1 patients (even within families and for the same underlying mutation) but they remain constant for the individual patients over time [48]. This indicates that in addition to the SPT mutations, also other factors are involved in determining plasma 1-deoxySL levels.

1-deoxySL were shown to induce disruption of neuronal cytoskeleton structures in cultured neuronal cells and induce dose-dependent reduction in neurite length [67].

1-deoxySL formation is suppressed at elevated L-serine concentrations, which was successfully demonstrated in several preclinical and clinical studies. Oral L-serine supplementation as a therapy in HSAN1 was first successfully tested in a preclinical study using a transgenic HSAN1 mouse model and subsequently confirmed in a single case study [5] and a 10-week HSAN1 pilot study with 20 HSAN1 patients [28]. L-Serine supplementation significantly reduced plasma 1-deoxySL levels in both, mice and humans and resulted in improved nerve function in the treated mice [28]. In contrast, mice on an L-alanine enriched diet had further increased 1-deoxySL levels, and developed a severe neuropathy with earlier onset and pronounced sensory loss [28]. Recently, a two-year placebo controlled clinical trial with L-serine was completed [27]. Although the primary endpoint of the study was not met, the results showed a significant improvement in the Charcot-Marie-Tooth neuropathy score (v2) with minimal side effects [27].

2.3. Guillain–Barre syndrome (GBS)

A special condition in which sphingolipids are involved is the Guillain–Barré syndrome (GBS). This inflammatory neuropathy includes autoimmune neuritis as well as neuritis directly related to infections of the nerve [94]. It is the most common and most severe acute paralytic neuropathy, with about 100 000 people developing the disorder worldwide every year. GBS can be divided into acute inflammatory demyelinating polyradiculoneuropathy (AIDP), axonal forms such as acute motor axonal neuropathy (AMAN) as well as acute motor and sensory axonal neuropathy (AMSAN) subgroups. The most common form of the disease is AIDP, which presents as progressive motor weakness, usually beginning in the legs and advancing proximally. Symptoms typically peak within four weeks, and then reach a plateau before resolving. More than one-half of the patients experience severe pain, and about two-thirds have autonomic symptoms, such as cardiac arrhythmias, blood pressure instability, or urinary retention. Nerve conduction studies show a slowing, or even possible blockage, of conduction.

GBS is caused by autoantibodies that bind to GM1, GD1a, GT1a, and GQ1b gangliosides at the nodes of Ranvier. This activates the complement system and disrupt sodium-channel clusters and axo-glial junctions, which leads to nerve conduction failure and muscle weakness.

Several outbreaks of GBS have been reported in relation to C. jejuni infections [38]. A prospective case-control study in the UK showed that 27 (26 %) of 96 patients with GBS had a C. jejuni infection shortly before the onset of disease, compared with 2% in household controls and 1% in age-matched hospital control [70]. Intravenous immunoglobulin (IVIG) and plasma exchange have proven efficacious therapies for GBS in large randomized, controlled trials [69].

2.4. Diabetic neuropathy

Because of the rising prevalence of diabetes, diabetic peripheral neuropathy (DPN) has become the most frequent form of peripheral neuropathies. Earlier studies showed that 66 % of patients with type 1 diabetes and 59 % of patients with type 2 diabetes developed some form of neuropathy [22]. Currently, the prevalence of neuropathy in adult diabetic patients is estimated at 50 % [40]. Based on the clinical appearance and distribution, DPN can be grouped into symmetric sensorimotor polyneuropathy, small-fiber, autonomic or acute motor neuropathy.

Length-dependent sensorimotor peripheral neuropathy is evident in 8% of the patients at the time of diagnosis [66] but increases in frequency with disease duration from 30 % to 66 % [66], also depending on whether the neuropathy is defined by clinical or electrophysiologic criteria.

Generally, the duration and level of hyperglycemia are important determinants of diabetes associated complications, including neuropathy [2]. The Diabetes Control and Complications Trial (DCCT) reported a 60 percent reduction in neuropathy in intensively treated groups after five years but the cumulative incidence of neuropathy (15–21 percent) and abnormal nerve conduction (40–52 percent) remained substantial [2]. Such findings suggested that neuropathy could develop despite intensive control of the glucose level. Thus, risk factors besides hyperglycemia are probably also involved in the evolution of DPN.

In particular dyslipidemia appears to be a relevant factor in DPN which might be linked to endothelial dysfunction and oxidative stress in the DRGs of sensory neurons [90]. In T1DM, elevated levels of low-density lipoprotein (LDL), total cholesterol, and triglycerides have been shown to be associated with DPN [87]. In T2DM, low HDL levels [18,88] have also been reported to influence the development of DPN. In contrast, other studies have not demonstrated an association between LDL or HDL and neuropathy [15,16,30]. The influence of triglycerides with DPN has been evaluated for T1DM (40) and T2DM [18,79,88,95]. For patients with mild to moderate diabetes, a correlation between the loss of myelinated fibers and triglyceridemia was observed. This association was independent of disease duration, age and diabetes control [93]. Another study demonstrated that lower extremity amputations, which are highly associated with neuropathy, were more frequent in diabetic subjects with elevated triglyceride levels [14]. Other studies showed that obesity is associated with DPN in both T1DM [20,87] and T2DM [84,88] and a recent study revealed that the prevalence of DPN was higher in obese patients compared to lean controls, even in those individuals with normoglycemia [15].

Interestingly, plasma 1-deoxySLs levels correlate closely with plasma triglycerides [64]. Although metabolically not directly interlinked, it appears that 1-deoxySL formation is driven by elevated triglyceride levels [91]. Several clinical studies showed that 1-deoxySLs are altered in metabolic diseases like the metabolic syndrome and T2DM [10,58,64]

and a recent study showed that 1-deoxySLs are long-term predictive biomarkers for the incidence of T2DM in an asymptomatic population. Even after adjusting for fasting glucose, 1-deoxySLs remained predictive for T2DM in a binary regression analysis [58].

Given the neurotoxicity of 1-deoxySLs in HSAN1, it is intriguing to hypothesize that these neurotoxic lipids are also involved in the etiology of the DPN. There is a surprising similarity in the clinical symptoms between HSAN1 and diabetic neuropathy [10,21]. DPN patients suffer from similar symptoms such as peripheral sensory loss and autonomous features, neuropathic pain and slow healing wounds.

So far, there is no effective therapy available for DPN. Given the rising number of individuals with T2DM worldwide, an effective therapy for DPN is a globally unmet medical need. It is therefore promising, that oral L-serine supplementation in diabetic rats not only effectively suppressed plasma 1-deoxySLs levels but also significantly improved sensory nerve function in these animals, without affecting hyperglycemia or triglyceride levels [63]. In addition, 1-deoxySLs might be causally involved in the progression of T2DM, as 1-deoxySA impairs β-cell function and insulin secretion in vitro [99].

2.5. Toxic neuropathies

Many environmental or nutritional agents and numerous drugs can cause a peripheral neuropathy [41,72]. Chronic alcoholism accounts for many cases of distal symmetric neuropathy. Also drugs such as amiodarone or antimicrobial agents such as isonizide and chloroquine, heavy metals (e.g., lead, arsenic, mercury) and industrial compounds, including n-hexane, acrylamide and organophosphates are common causes for toxic neuropathies which mostly lead to primary axonal damage [41,72].

A special situation is the chemotherapy-induced toxic peripheral neuropathy (CIPN) which is a common and dose-limiting side effect for various cytostatic drugs. This includes drugs such as bortezomib, platinum derivates, taxanes, and vinca alkaloids [17]. Patients' symptoms include pain, numbness, tingling and burning sensations, and motor weakness in the extremities.

Interestingly, neuropathy symptoms of patients treated with paclitaxel are also associated with increased plasma 1-deoxySL formation [47]. This was recently confirmed in mice treated with docetaxel which showed significantly elevated 1-deoxySLs in dorsal root ganglia (DRG) after drug treatment [7]. Earlier studies showed that paclitaxel-induced neuropathy is associated with a reduced L-serine supply to dorsal root ganglia from the surrounding satellite cells [44]. The intraperitoneal administration of L-serine in paclitaxel treated mice improved nerve conductance and paclitaxel-induced mechanical allodynia/hyperalgesia [44]. Unfortunately, 1-deoxySL levels were not analyzed in these mice.

3. Conclusions

Among the different lipid classes, primarily SL seem to be relevant in neurological disorders. A special role in this context seem to have 1-deoxySL that are formed in an alternative reaction during sphingolipid de-novo synthesis. Pathological changes in 1-deoxySL formation are conclusively linked to HSAN1 but also appear to be involved in other conditions such as the diabetic or chemotherapy induced neuropathy. Currently, there is only limited therapeutic options for the treatment of peripheral neuropathies. Serine supplementation was demonstrated to be effective in lowering 1-deoxySL levels and is applied therapeutically in HSAN1. Aside from GBS, IVIG is also used for the treatment of other neurological disorders including dermatomyositis, chronic inflammatory demyelinating polyneuropathy (CIDP), multifocal motor neuropathy (MMN), myasthenia gravis and stiff person syndrome [52]. Therefore and in the long term, a detailed understanding of the underlying pathomechanism(s) and of the relevant neurotoxic factors that cause peripheral neuropathies is important to develop more targeted and mechanism-based therapies.

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